

## **I. REMARKS**

First, applicants take this opportunity to thank the Examiner for his participation in the in-person interview on April 15, 2011 with applicants' representatives. The remarks and amendments presented herein are consistent with what was discussed and agreed to in the interview. As such, applicants believe this application is in condition for allowance.

Upon entry of the claim amendments, claims 1-8, 10, 12-20, 43-46 and 48-60 will be pending in the present application. In this amendment, claims 1 and 12 have been amended, claims 9 and 47 have been canceled without prejudice to or disclaimer of the subject matter contained therein, and new claims 48-60 have been added. Claims 11 and 21-42 were previously cancelled.

Claim 1 has been amended to recite "A method for treating a respiratory disease in a child patient while reducing or avoiding systemic side effects ~~associated with inhaled or intranasal corticosteroids in said patient, which patient is a child and the method comprises on said child's growth rate, comprising~~ administering to the patient child a dose of a composition containing ciclesonide as the sole active ingredient, or a pharmaceutically acceptable salt thereof, wherein the dose of the composition comprises ciclesonide in an amount of from 20 to 200 µg, and wherein ciclesonide consists essentially of its R-epimer."

Basis may be found in previously pending claim 9 and in the instant specification at page 8, final two paragraphs, for the claim limitation regarding growth rate.

Basis for new claim 48, dependent from claim 45, may be found in the instant specification on page 6, 6<sup>th</sup> paragraph.

Basis for new claim 49, dependent from claim 1, may be found in the instant specification on page 3, 3<sup>rd</sup> paragraph.

Basis for new claims 50-52, each dependent from claim 1, may be found in the instant specification on page 3, 4<sup>th</sup> paragraph.

Basis for new claims 53-55, dependent from claims 1-3, respectively, may be found in the instant specification on page 3, 2<sup>nd</sup> paragraph.

Basis for new claim 56, dependent from claim 1, may be found in the instant specification on page 3, 2<sup>nd</sup> paragraph.

Basis for new claims 57-58, each multi-dependent from claims 13-16, may be found in the instant specification on page 3, 6<sup>th</sup> paragraph and page 4, 2<sup>nd</sup> paragraph.

Basis for new claim 59, dependent from new claim 51, may be found in the instant specification on page 3, 2<sup>nd</sup>, 4<sup>th</sup> and 6<sup>th</sup> paragraphs and page 4, 2<sup>nd</sup> paragraph.

Basis for new claim 60, dependent from claim 15, may be found in the instant specification on page 3, 2<sup>nd</sup>, 4<sup>th</sup> and 6<sup>th</sup> paragraphs and page 4, 2<sup>nd</sup> paragraph.

All claims depend, either directly or indirectly, from claim 1. Therefore, no new matter is presented and entry of the amendments is respectfully requested.

**II. REJECTIONS UNDER 35 USC § 103(a)**

**A. REJECTION OF CLAIMS 1-10, 12, 13, 19, 20 AND 47**

At page 4 of the Official Action, the Examiner has rejected claims 1-10, 12, 13, 19, 20 and 47 under 35 USC § 103(a) as being unpatentable over Postma et al., Dubus et al., Belvisi et al. and Agertoft et al.

**RESPONSE**

As a preliminary matter, as noted in the Interview Summary, the Examiner erroneously cited a 1994 Agertoft reference, but supplied and relied on an Agertoft reference published in 2000. Therefore, applicants' arguments have been based on the teachings contained in the 2000 Agertoft reference.

Also, claims 9 and 47 have been canceled without prejudice or disclaimer with the amendment submitted herewith, thereby rendering the basis for this rejection moot to these claims.

As to claims 1-8, 10, 12, 13, 19 and 20, the rejection is respectfully traversed. The Examiner has not established a *prima facie* case of obviousness against the presently pending claims.

To establish a *prima facie* case of obviousness, the PTO must satisfy three requirements. First, there must be some motivation or teaching in the references cited by the Examiner to combine the separate elements taught in the separate references. As the U.S. Supreme Court held in *KSR International Co. v. Teleflex Inc. et al.*, 550 U.S. 398 (2007), "a court must ask whether the improvement is more

than the predictable use of prior art elements according to their established functions. ...it [may] be necessary for a court to look to interrelated teachings of multiple patents; the effects of demands known to the design community or present in the marketplace; and the background knowledge possessed by a person having ordinary skill in the art, all in order to determine whether there was an apparent reason to combine the known elements in the fashion claimed by the patent at issue. ...it can be important to identify a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed new invention does... because inventions in most, if not all, instances rely upon building blocks long since uncovered, and claimed discoveries almost of necessity will be combinations of what, in some sense, is already known.” See *KSR International Co. v. Teleflex Inc. et al.*, 550 U.S. 398 at 417-418. Second, the proposed modification of the prior art must have had a reasonable expectation of success, determined from the vantage point of the skilled artisan at the time the invention was made. *Amgen Inc. v. Chugai Pharm. Co.*, 18 USPQ2d 1016, 1023 (Fed. Cir. 1991). Lastly, the prior art references must teach or suggest all the limitations of the claims. *In re Wilson*, 165 USPQ 494, 496 (C.C.P.A. 1970).

Presently pending claim 1 is directed to a “method for treating a respiratory disease in a child while reducing or avoiding systemic side effects on said child’s growth rate, comprising administering to the child a dose of a composition containing ciclesonide as the sole active ingredient, or a pharmaceutically acceptable salt

thereof, wherein the dose of the composition comprises ciclesonide in an amount of from 20 to 200 µg, and wherein ciclesonide consists essentially of its R-epimer."

The four cited references do not establish a *prima facie* case of obviousness over the presently pending claims because, at a minimum, the references do not "teach or suggest all the limitations of the claims" per *In re Wilson*.

In particular, Postma et al. is relied on for its alleged teaching of the equi-effectiveness of budesonide and ciclesonide. However, Postma et al. does not teach the equi-effectiveness of budesonide and ciclesonide. Instead, Postma et al. hypothesize that *morning and evening dosing of ciclesonide may be equi-effective* because a similar study showed that *morning and evening dosing of budesonide showed equi-effectiveness*. Postma et al. never compares budesonide and ciclesonide for their equi-effectiveness. Instead, Postma et al. separately look at morning and evening *dosing* of these active ingredients and whether the *dosing* of the same active ingredient would be as effective in the morning as compared to the evening and vice-versa. Thus, Postma et al. cannot be relied on to demonstrate the equi-effectiveness of budesonide and ciclesonide as active ingredients.

Dubus et al. is relied on to demonstrate that any inhaled corticoid at a dosage of 400µg or less per day dosage would not have any significant systemic effect. However, a closer reading of the bibliographic references that are referred to by Dubus et al. to establish this general conclusory statement clearly shows that no singular microgram dosing threshold can be established for all inhaled corticoids. Thus, the general, conclusory statement made by Dubus et al. regarding all inhaled

corticoids at a daily dosage below 400µg not having any significant systemic effects is not a predictable result and cannot be true.

In this regard, applicants have submitted herewith in a supplemental IDS the two bibliographic references cited by Dubus et al. to demonstrate the inaccuracy of the statement made by Dubus et al. and relied on by the Examiner. In particular, *"Early intervention for childhood asthma: Inhaled glucocorticoids as the 'preferred' medication"* (1998) to Szeffler and *"Inhaled steroids in children: Risks versus rewards"* (1998) to Wagener et al. have been submitted herewith.

As discussed in the Examiner interview, neither Szeffler nor Wagener et al. contain any teaching whatsoever to establish such a 400µg threshold for the appearance of systemic effects. Further, the true teachings of the Wagener et al. reference particularly undermine the Dubus et al. statement regarding the singular 400µg threshold dosing of inhaled corticoids and possible systemic effects resulting from such a dose.

In particular, Wagener et al. clearly demonstrates that what is considered to be a "low" dose for one inhaled corticoid may be considered "high" for a different inhaled corticoid and vice-versa. (See, Wagener et al., Table, p. 382). For example, triamcinolone acetonide has a "low" daily dosage of less than or equal to 800µg, while fluticasone propionate has a "low" daily dosage of less than or equal to 176µg – over 4.5 times LESS than the triamcinolone acetamide species. Likewise, fluticasone propionate has a "high" daily dosage of greater than or equal to 440µg – which is about HALF of the "low" dosage of the triamcinolone acetamide species.

In view of the teachings of Wagener et al. that "[r]isks are minimal for patients receiving low doses (Table) but can be substantial with high doses", (See Wagener et al., page 382, col. 2, 3<sup>rd</sup> paragraph), it is clearly impossible for Dubus et al. or anyone else to dictate a singular microgram threshold for all inhaled corticoids as to what may have a "significant systemic effect" and what may not. As clearly shown in the Table of Wagener et al., each inhaled corticoid requires *different* amounts to achieve the desired effect of treating asthma in children.

As such, the improper conclusory statement made by Dubus et al. is an improper mischaracterization of the true teachings of the Wagener et al. and Szeffler references. Therefore, Dubus et al. cannot be properly relied on for the concept that inhaled corticoids "are widely recommended for controlling pediatric asthma and that 400µg or less per day dosage do not have significant systemic effect" as outlined in the Official Action on page 5.

Regarding the Belvisi et al. reference, applicants respectfully submit that this reference is not prior art against the present application. The Official Action on page 4 alleges a publication date of Belvisi et al. in March 2003. However, as discussed in the interview, and agreed to by the Examiner as outlined in the Interview Summary, Belvisi et al. was published in December 2003 and was available on-line in October 2003. As the earliest priority date of the present application is September 16, 2003, this reference is not prior art.

Regarding Agertoft et al. (2000), applicants respectfully submit that this reference reports 10-year growth data for asthmatic children who have taken

budesonide and have reached adult height. In particular, this reference teaches that a mean daily dose of budesonide at 412µg does not negatively impact an asthmatic child's ability to reach normal adult height long term. However, Agertoft et al. (2000) do state that "growth rates were significantly reduced during the first years of budesonide treatment" (See abstract). Agertoft et al. (2000) contains no teaching whatsoever regarding the presently claimed ciclesonide.

To briefly summarize:

- Postma does not teach the equi-effectiveness of budesonide and ciclesonide as alleged in the Official Action;
- Dubus et al. does not properly teach the concept that a dose of 400µg or less per day of any inhaled corticoid has no significant systemic effect as put forth in the Official Action;
- Belvisi et al. is not prior art against the present application; and
- Agertoft et al. (2000) does not teach ciclesonide nor any systemic effects associated with the administration of ciclesonide, but instead teach that budesonide treatment leads to significantly reduced growth rates.

As such, the cited references cannot establish a *prima facie* case of obviousness over the presently pending claims.

Thus, presently pending claim 1, which is directed to:

"A method for treating a respiratory disease in a child while reducing or avoiding systemic side effects on said child's growth rate, comprising administering to the child a dose of a composition containing ciclesonide as the sole active ingredient, or a pharmaceutically acceptable salt thereof, wherein the dose of the composition comprises ciclesonide in an amount of from 20 to 200 µg, and wherein ciclesonide consists essentially of its R-epimer" is patentable over the cited references. All



pending claims of this application either directly or indirectly depend from claim 1, and are also therefore patentable over the cited references.

Applicants take this opportunity to point out the Examiner's statement in the Interview Summary agreeing that these arguments regarding the presently claimed subject matter "are sufficient to overcome the rejections of record."

Reconsideration and withdrawal of this rejection is respectfully requested.

**B. REJECTION OF CLAIMS 1-10, 12-16, 19, 20 AND 43-47**

At page 6 of the Official Action, the Examiner has rejected claims 1-10, 12-16, 19, 20 and 43-47 under 35 USC § 103(a) as being unpatentable over Postma et al., Dubus et al., Belvisi et al. , Agertoft et al. and Oliver et al.

**RESPONSE**

Applicants respectfully note that claims 9 and 47 have been canceled without prejudice or disclaimer with the amendment submitted herewith, thereby rendering the basis for this rejection moot to these claims.

Regarding the remaining claims, the rejection is respectfully traversed. The Examiner has not established a *prima facie* case of obviousness against the presently pending claims.

The requirements for establishing a *prima facie* case of obviousness are outlined above in section II. A., and for the sake of brevity, applicants incorporate by reference these requirements into the present discussion of the Oliver et al.

reference. Applicants also incorporate by reference the discussion of the Postma et al., Dubus et al., Belvisi et al. and Agertoft et al. references discussed above in section II. A.

Oliver et al. does nothing to remedy the deficient teachings of the Postma et al., Dubus et al., Belvisi et al. and Agertoft et al. references discussed above in section II. A. In particular, as conceded by the Examiner on page 3 of the Final Official Action mailed December 28, 2009, Oliver et al. does not teach the administration of ciclesonide to children.

Therefore, the five references relied on by the Examiner in this rejection do not establish a *prima facie* case of obviousness against the presently pending claims.

Applicants take this opportunity to point out the Examiner's statement in the Interview Summary agreeing that these arguments regarding the presently claimed subject matter "are sufficient to overcome the rejections of record."

Reconsideration and withdrawal of this rejection is respectfully requested.

**C. REJECTION OF CLAIMS 1-10, 12-13 AND 17-21**

At page 7 of the Official Action, the Examiner has rejected claims 1-10, 12-13 and 17-21 under 35 USC § 103(a) as being unpatentable over Calatayud et al., Dubus et al., Agertoft et al. and Belvisi et al.

**RESPONSE**

Applicants respectfully note that claim 9 has been canceled without prejudice or disclaimer with the amendment submitted herewith, thereby rendering the basis for this rejection moot to this claim.

Regarding the remaining claims, the rejection is respectfully traversed. The Examiner has not established a *prima facie* case of obviousness against the presently pending claims.

The requirements for establishing a *prima facie* case of obviousness are outlined above in section II. A., and for the sake of brevity, applicants incorporate by reference these requirements into the present discussion of the Calatayud et al. reference. Applicants also incorporate by reference the discussion of the Dubus et al., Belvisi et al. and Agertoft et al. references discussed above in section II. A.

Calatayud et al. does nothing to remedy the deficient teachings of the Dubus et al., Belvisi et al. and Agertoft et al. references discussed above in section II. A. In particular, as conceded by the Examiner on page 8 of the present Official Action, Calatayud et al. does not teach the administration of ciclesonide to children.

Therefore, the references relied on by the Examiner do not establish a *prima facie* case of obviousness against the presently pending claims.

Applicants take this opportunity to point out the Examiner's statement in the Interview Summary agreeing that these arguments regarding the presently claimed subject matter "are sufficient to overcome the rejections of record."

Reconsideration and withdrawal of this rejection is respectfully requested.

### III. CONCLUSION

Applicants assert that the claims are in condition for immediate allowance and early notice to that effect is earnestly solicited. Should the Examiner deem that any further action by Applicants' undersigned representative is desirable and/or necessary, the Examiner is invited to telephone the undersigned at the number set forth below.

Applicants authorize the Director to charge any fee deficiency or credit any overpayment to Deposit Account No. 14-0112.

Respectfully submitted,

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